REMARKS

Claims 1-36 are pending in this application. Claims 1-36 have been cancelled. New Claims 37-66 have been added. New Claims 37-55 are directed to methods for determining the health of a subject's prostate, new Claims 56-64 are directed to methods for determining the presence of prostate cancer in a subject, and new Claims 65 and 66 are directed to methods for determining the efficacy of prostate cancer treatment. In particular, new independent Claims 37 and 56 incorporate *inter alia* some of the limitations of cancelled Claims 1, 20, and 22. And new independent Claim 65 incorporates *inter alia* some of the limitations of cancelled Claims 24, 34, 35, and 36. No new matter has been added. Upon entry of this Amendment and Response, Claims 37-66 will be pending in this Application.

Species Election Requirement

The Examiner has made the species election final but has stated that if the elected species is not found, the search will be expanded to cover additional non-elected species (namely new Claims 44 and 45) in accordance with MPEP §803.02.

Rejection Under 35. U.S.C. §112, second paragraph

Claims 30-32 (now Claims 61-63, respectively) are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. In particular, the Office Action alleges there is insufficient antecedent basis for various limitations in Claims 30-32.

Claims 30-32 have been cancelled and new Claims 61-63 that are dependent on new Claim 56 render this rejection moot.

Rejection Under 35. U.S.C. §102(b)

Claims 1-3, 5, 9, 13-16, and 20-23 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by U.S. Patent No. 5,188,816, issued to Sherry et al. (the "Sherry et al. Patent"). In particular, the Office Action alleges:

> Sherry discloses phosphorous containing macrocyclic chelates which bind certain biological ions with relative specificity. The ^{31}P resonance of these chelators shift to a new position in the NMR spectrum when a metal ion occupies the cavity of the chelate and the NMR chemical shift of the bound chelate differs for each metal ion. Intracellular concentration of Mg^{2+}, Ca^{2+}, Zn^{2+} may be monitored by ^{31}P NMR (column 1, lines 1-40). The invention also relates to NMR imaging of living subjects, sometimes referred to as magnetic resonance imaging, MRI (column 2, lines 1-22). NMR is an advantageous method for producing cross-sectional images of the human body

(column 2, lines 40-42). See column 10 for relative stability of various metal ions and k values. The NMR/MRI scanning disclosed by Sherry would necessitate acquisition, generating and correlating steps in claim 1, as these steps are part of such scanning to provide the image, as related to metal ion concentration, disclosed by Sherry.

Page 4 of the Office Action.

While cancellation of Claims 1-3, 5, 9, 13-16, and 20-23 renders this rejection moot, to the extent that the Examiner believes rejection under 35 U.S.C. §102(b) is applicable to any of the new Claims the undersigned submits the following arguments.

It is well recognized that claims are anticipated if, and only if, each and every element as set forth in the claim is found in a single prior art reference. Moreover the identical invention must be shown in as complete detail as is contained in the claim. See, for example, *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913 (Fed. Cir. 1989)

In contrast to the Sherry et al. Patent which uses ^{31}P NMR, pending Claims are directed to methods that use fluorine MRI. Since elements of the pending claims are not disclosed in the Sherry et al. Patent, it is submitted that the rejection under 35 U.S.C. §102(b) is improper. Accordingly, it is respectfully requested that the rejection of claims under 35 U.S.C. §102(b) be withdrawn.

Rejection Under 35. U.S.C. §103(a)

Claims 1, 2, 4-6, 9 and 13-16 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Song et al., *Am. J. Physiol. Cell Physiol.*, **1995**, *269*, C318-C322 (the "Song et al. Reference") in view Mason et al., *Magn. Res. Imaging*, **1989**, *7*(5), p. 475-85 (abstract) the "Mason et al. Reference").

Claims 1-6, 9, 13-19, 24, 25, and 29-33 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the Song et al. Reference in view the Mason et al. Reference further in view of Csermely et al., *Biochem. Biophys. Res. Commun.*, **1989**, *165*(2), p. 838-844 (abstract) (the "Csermely et al. Reference").

Claims 1-6 and 9-36 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the Song et al. Reference and the Mason et al. Reference in view of the Csermely et al. Reference further in view of U.S. Patent No. 5,707,605, issued to Meade (the "Meade Patent")

and U.S. Patent Application Publication No. 2002/0114848 by Woods (the "Woods Patent Application").

In particular, the Office Action alleges the following are disclosed by the cited references: (1) The Song et al. Reference:

> discloses measurement of intracellular calcium concentration in vivo and in situ using ^{19}F-NMR and 5f-BAPTA.

Page 5 of the Office Action; (2) the Mason et al. Reference:

> teaches that ^{19}F spin-echo magnetic resonance imaging can be performed in vivo, and can be used to delineate concentration/anatomic distribution of contrast agent in vivo….

Page 7 of the Office Action; (3) the Csermely Reference:

> discloses that increasing interest is focused on the role of zinc in biological systems…. It would have been further obvious to provide in vivo determination/imaging of zinc concentration, rather than calcium, when the teachings of Song and Mason are taken in view of Csermely. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because Csermely teaches that increasing interest is focused on the role of zinc in biological systems, and because it was determined that zinc forms complexes with 5-F-BAPTA having higher kinetic and thermodynamic stability than calcium complexes, as measured by ^{19}F NMR.

Page 8 of the Office Action; (4) the Meade Patent:

> discloses magnetic resonance imaging agents comprising a paramagnetic metal ion bound to a complex wherein said complex comprises a chelator and a blocking moiety covalently attached to said chelator which binds in at least a first coordination site of said metal ion and which is capable of interacting with a target substance such that the exchange of water in at least said first coordination site is increased (abstract). A blocking moiety may be a calcium binding substance such as known in the art (such as BAPTA), and the target substance may be Ca^{2+}, Mg^{2+}, Zn^{2+}, Na^{+}. The metabolite may be associated with a particular disease or condition within an animal. For example, BAPTA-DOTA derivatives may be used to **diagnose Alzheimer's disease or other neurological disorder**….

(Emphasis added), Page 9 of the Office Action; and (5) the Woods Patent Application:

> discloses methods for regulating levels of zinc, cadmium and calcium in humans and for diagnosing, or screening for the risk of developing, diseases associated with abnormal levels of cadmium, zinc and calcium in body fluids and tissues (title). **Diseases associated with unbalanced levels of cadmium and/or unregulated levels of zinc or increased levels of zinc-containing or PGE2-dependent matrix metalloproteinases** in body fluids include diabetes, osteoporosis, Alzheimer's disease, hypertension and cancers, such as prostate cancer, colon cancer and breast cancer….

(Emphasis added), Pages 9-10 of the Office Action.

With regards to detecting prostate cancer, crux of the rejection under 35 U.S.C. §103(a) appears to be that:

> It would have been … obvious to diagnose a disease state via ^{19}F MRI imaging of metal ion concentration using F-BAPTA, wherein the concentration of a target metal ion is characteristic of

> the presence or absence of the disease state, when the teachings of Song, Mason and Csermely are taken in view of Meade and Woods. One would have been motivated to do so because Meade teaches that calcium/zinc can be detected in vivo via MRI using BAPTA chelators, and may be used for imaging Alzheimer's. Since BAPTA chelators have been used to detect ion concentration in vivo (Ca, Zn), and to image Alzheimer's, one of ordinary skill would have had a reasonable expectation of success in imaging Alzheimer's or prostate cancer upon ^{19}F MRI detection of F-BAPTA, **since Woods teaches that diseases associated with unbalanced levels of zinc include Alzheimer's and prostate cancer**.

(Emphasis added). Page 10 of the Office Action.

The Meade Patent, as discussed in paragraphs [0023] to [0026] of the present Application involves **proton magnetic resonance** and the use of blocked paramagnetic contrast agents, which typically contain paramagnetic ions, often toxic gadolinium ions. More significantly, the Meade Patent, as acknowledged in the Office Action, is *inter alia* directed to diagnosing Alzheimer's disease or other neurological disorder. The latter difference renders the Meade Patent irrelevant with regards to the amended claims since the amended claims are directed to determining the health of prostate.

The Woods Patent Application discuses *inter alia* various methods involving unbalanced levels of cadmium, zinc, and the zinc:cadmium ratio **in a body fluid**. In particular, the Woods Patent Application states:

> **[0002]** … methods for **regulating levels of cadmium, zinc and calcium** in the human body. More specifically, the invention relates to **methods for decreasing PGE2:PGF2α ratios and regulating zinc:cadmium ratios** and for regulating the concentration of zinc-containing and PGE2-dependent matrix metalloproteinases in humans.
>
> **[0003]** The invention further relates to methods of screening for the presence of, or risk of developing, a disease associated with **unbalanced levels of cadmium** in a body fluid, body fluid component or tissues of a human. The invention also relates to methods for delaying or preventing the onset of a disease in a human, wherein **the disease is associated with unbalanced levels of cadmium and unregulated levels of zinc in body tissues and fluids, by balancing the levels of cadmium and regulating the levels of zinc in the body tissues and fluids of the human**.
>
> …
>
> **[0018]** In accordance with the present invention, **methods and compositions are provided for decreasing PGE2:PGF2α and regulating zinc:cadmium ratios and regulating the concentration of zinc-containing and PGE2-dependent matrix metalloproteinases** in the body of a human. Methods and compositions also are provided for regulating calcium levels in the fluids and tissues in the body of a human. Elevated or otherwise unregulated levels of PGE2, zinc and calcium and elevated or otherwise unregulated concentrations of zinc-containing and PGE2-dependent matrix metalloproteinases have been found to be associated with the development of certain diseases, including prostate cancer, colon cancer, breast cancer, Alzheimer's disease, hypertension, osteoporosis and diabetes. For example, studies have found

that patients with diabetes typically have elevated levels of zinc in their urine (104), and osteoporosis also has been associated with increased urinary zinc excretion (101). Zinc levels also have been shown to be elevated in the red blood cells and urine of persons suffering from cardiovascular disease; there is a decreased movement of zinc out of red blood cells, an increased movement of zinc into red blood cells and an increased excretion of zinc from the body. By regulating the concentration of zinc and PGE2 in the person's body, one can delay or prevent the onset of, or treat the development of, these diseases. **Furthermore, it has been found that changes in cadmium and zinc levels also are associated with changes in calcium levels in the body. As cadmium regulates zinc, both cadmium and zinc regulate calcium. Unbalanced levels of cadmium lead to unregulated levels of zinc, which in turn leads to unregulated levels of calcium.**

[0019] It also has been discovered that **populations which have a high incidence of diseases such as prostate or breast cancer, hypertension, diabetes, osteoporosis and Alzheimer's also often have diets low in cadmium and unbalanced levels of cadmium in their body fluids**, components of body fluid and tissues. For instance, a number of studies have found that cadmium levels are low in the cerebrospinal fluid of Alzheimer's patients. Accordingly, further in accordance with the present invention, methods are provided for screening persons to determine an indication of the presence of, or their risk of developing, a disease associated with unbalanced levels of cadmium in their body fluids, body fluid components, and tissues.

…

[0021] In another embodiment of the invention, there is provided a method of **balancing the amount of cadmium in the body fluids and/or tissues of a human which comprises administering to the human one or more cadmium salts in an amount sufficient to balance the concentration of cadmium per se and to regulate the concentration of zinc relative to the concentration of cadmium** in the body fluids and/or tissues of the human.

[0022] In another embodiment of the present invention, there is provided **a method for regulating the zinc:cadmium ratio** in the body fluid or tissues of a human **which comprises regulating the concentration and activity of zinc in the body fluid of the human by administering to the human one or more cadmium salts**.

[0023] In a further embodiment, there is provided **a method of regulating the concentrations of zinc and zinc-containing and PGE2-dependent matrix metalloproteinases in a human by administering one or more cadmium salts.**

…

[0035] …. **The reduction of function with cadmium deficiency in man is manifest with prostate cancer**, hypertension and other diseases (97). Foods that are high in cadmium, such as leafy vegetables, cereals and grains, are associated with a lowered incidence of prostate cancer and hypertension.

[0036] Although not wishing to be bound by theory, it is believed that one **biological role of cadmium is to regulate zinc homeostasis** by decreasing zinc excretion in urine. It appears that cadmium acts as a regulator of zinc. When the level of cadmium is out of balance (i.e., if there is a cadmium deficiency), the levels of zinc cannot be regulated properly. In a healthy person, the concentration of zinc in the cells of tissues typically is high relative to that of cadmium; cadmium levels are lower relative to the levels of zinc in fluids. Thus, in a healthy person, the zinc:cadmium ratio is relatively high in cells and lower in fluids…. It is proposed that an **underlying cause of certain diseases is a deficiency of cadmium** leading to an increased urinary excretion of zinc and a secondary zinc deficiency.

(Emphasis added).

As can be seen above, crux of the methods discussed in the Woods Patent Application is the amount of cadmium in a body fluid and the amount of zinc is only an effect due to the level of cadmium. Thus, the Woods Patent Application discusses regulating the amount of zinc by controlling the amount of cadmium. See, for example, paragraph [0019] ("populations which have a high incidence of diseases such as prostate or breast cancer … also often have diets low in cadmium and **unbalanced levels of cadmium** in their **body fluids**…."). (Emphasis added). More significantly, the "unbalanced level of cadmium and/or zinc" referred to in the Woods Patent Application refers to the "unbalanced levels" as they relates to the level of cadmium and/or zinc in **a body fluid**. For example, the Woods Patent Application states:

> **[0042]** Thus, in accordance with one embodiment of the present invention, it now has been found that **a person can be screened for an indication of or risk of developing a disease** associated with unbalanced levels of cadmium in body fluids and tissues **by measuring the level of cadmium, or the level of zinc, in a sample of his or her body fluid**….
>
> **[0043]** **The body fluid assayed can include serum or urine or, if the patient is a man, his seminal plasma. It is preferred to assay either urine or seminal plasma**….
>
> **[0044]** In accordance with this invention, **the level of cadmium in a person's body fluid can be measured simply by taking a measure of the amount of cadmium in the selected body fluid**…. by measuring the level of cadmium in a sample of his or her red blood cells, urine or, **if the person is male, in his seminal fluid**.
>
> **[0045]** A person is considered to be at risk for developing, or to be in the preliminary stages of developing, a disease, if the level of cadmium **in his or her body fluid** is more that about 15%, and preferably more than about 20%, below normal levels, or if the level of zinc **in his or her body fluid** is more than about 15%, and preferably more than about 20% above normal levels….
> …
>
> **[0051]** … Diseases associated with unbalanced levels of cadmium and/or unregulated levels of zinc or increased levels of zinc-containing or PGE2-dependent matrix metalloproteinases **in body fluids** include diabetes, osteoporosis, Alzheimer's disease, hypertension and cancers, such as prostate cancer, colon cancer and breast cancer.

(Emphasis added).

Thus, the Woods Patent Application discusses that the actual cause of prostate cancer is cadmium not zinc. More significantly, the Woods Patent Application explicitly states measuring the level of cadmium and/or zinc is a body fluid **not in prostate**.

It is well known to one skilled in the art that analytical methods for measuring a particular analyte in tissues or organs is typically different than methods for measuring the

analyte in a body fluid. For example, MRI is typically used to observe tissues or organs not body fluids. Since one skilled in the art would NOT typically use MRI to measure an analyte in a body fluid—especially due to its high cost—one skilled in the art would not be motivated to combine the teachings of the cited references in a manner suggested in the Office Action.

More significantly, in contrast to methods discussed in the Woods Patent Application, methods of the presently pending claims include acquiring magnetic resonance imaging of the subject's prostate not a body fluid.

In view of the above, it is submitted that (1) one skilled in the art would not be motivated to combine the teachings of the cited references in a manner suggested in the Office Action because MRI is typically not used to measure analytes in a body fluid, and more significantly (2) even if *arguendo* the teachings of the cited references are combined in a manner suggested in the Office Action, and the Applicant maintains there is no such motivation, the resulting method would utilize MRI to analyze a body fluid not prostate as claimed in the presently pending claims. Therefore, the rejections under 35 U.S.C. §103(a) are improper. Accordingly, it is respectfully requested that all of the rejections under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at (303) 955-8103.

Respectfully submitted
HAMILTON DESANCTIS & CHA
Customer Number: **68514**

Date: July 26, 2010

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